69068

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Patrick Lewis Examiner #: 79002 Date: 6-18-02
Art Unit: 1623 Phone Number 30 5-4043 Serial Number: 10/031,692
Mail Box and Bldg/Room Location: CM1/8D12 Results Format Preferred (circle): PAPER DISK E-MAIL
CM1/8B19

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Ceramide analogs, process for their preparation and their use as antitumor agents

Inventors (please provide full names): ~~Bruno~~ Bruno Macchia, Aldo Balsamo, Marco Macchia, Maria Del Tacca, Romana Danesi

Earliest Priority Filing Date: 7-22-99

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

= "Compounds of formula (I) according to claims 1 & 2

Key claims
1 + 2

Point of Contact:
Toby Port
Technical Info. Specialist
CM1 6A04
703-308-3534

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****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Toby + Alex	NA Sequence (#)		STN	27.00
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)	2	Questel/Orbit	
Date Searcher Picked Up: 6/18	Bibliographic		Dr.Link	
Date Completed: 6/20	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 30	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time: 60	Other		Other (specify)	

PTO-1590 (8-01)

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Patrick Lewis Examiner # : 79002 Date: 6-18-02
Art Unit: 1623 Phone Number 305-4643 Serial Number: 10/031,692
Mail Box and Bldg/Room Location: CM1/8D12 Results Format Preferred (circle): PAPER DISK E-MAIL
CM1/8B19

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Ceramide analogs, process for their preparation and their use as antitumor agents

Inventors (please provide full names): ~~Bruno~~ Bruno Macchia, Aldo Balsamo, Marco Macchia, Mario Del Tacca, Romano Danesi

Earliest Priority Filing Date: 7-22-99

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

- Compounds of formula (I) according to claims 1 + 2

Key claims
1 + 2

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher:	NA Sequence (#)	STN
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed:	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (8-01)

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FILE 'REGISTRY' ENTERED AT 10:23:35 ON 20 JUN 2002
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DICTIONARY FILE UPDATES:  18 JUN 2002  HIGHEST RN 431976-32-8

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

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Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L7                STR
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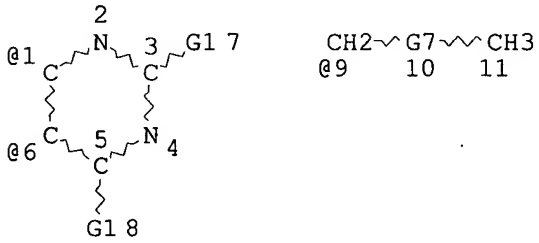

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
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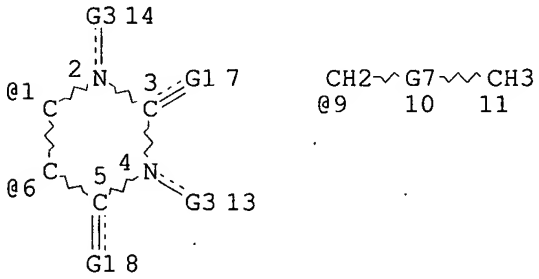

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STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01


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FILE COVERS 1907 - 20 Jun 2002  VOL 136 ISS 25
FILE LAST UPDATED: 18 Jun 2002  (20020618/ED)

  This file contains CAS Registry Numbers for easy and accurate
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information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.


L7              STR
L9           61 SEA FILE=REGISTRY SSS FUL L7
L16             STR
L18          45 SEA FILE=REGISTRY SUB=L9 SSS FUL L16
L19           6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L18


=> d ibib abs hitstr l19 1-6

L19  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:719208  CAPLUS
DOCUMENT NUMBER:          136:53590
TITLE:                    Design, Synthesis, and Characterization of the
```

Antitumor Activity of Novel Ceramide Analogues

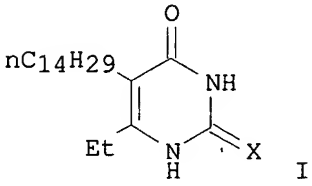
AUTHOR(S): Macchia, Marco; Barontini, Silvia; Bertini, Simone; Di Bussolo, Valeria; Fogli, Stefano; Giovannetti, Elisa; Grossi, Enzo; Minutolo, Filippo; Danesi, Romano

CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Pisa, Pisa, 56126, Italy

SOURCE: Journal of Medicinal Chemistry (2001), 44(23), 3994-4000
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



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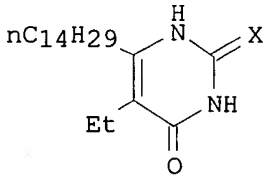


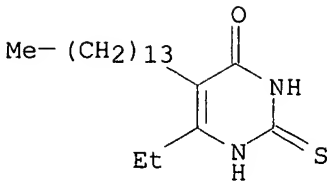
III

AB A deficiency in apoptosis is one of the key events in the proliferation and resistance of malignant cells to antitumor agents; for these reasons, the search for apoptosis-inducing drugs represents a valuable approach for the development of novel anticancer therapies. In this study we report the first example of conformationally restrained analogs of ceramide, where the polar portion of the mol. has been replaced by a thiouracil {[I; X = S (II)], [III; X = S (IV)]} or uracil I [X = O (V)], III [X = O (VI)] ring. The evaluation of their biol. activity on CCRF-CEM human leukemia cells demonstrated that the most active was II followed by V (mean 50% inhibition of cell proliferation [IC50] 1.7 and 7.9 .mu.M, resp.), while compds. IV and VI were inactive, as were uracil, thiouracil, and 5,6-dimethyluracil, the pyrimidine moieties of compds. II, IV-VI. For comparison, the IC50 of the ref. substance, the cell-permeable C2-ceramide, was 31.6 .mu.M. Compds. II and V and C2-ceramide were able to trigger apoptosis, as shown by the occurrence of DNA and nuclear fragmentation, and to release cytochrome c from treated cells. The treatment of female CD-1 nu/nu athymic mice bearing a WiDr human colon xenograft with the most active compd. II at 2, 10, 50, and 200 mg/kg i.p. daily for 10 days resulted in an antitumor effect that was equiv. at 50 mg/kg or superior (200 mg/kg) to that of cyclophosphamide, 20 mg/kg i.p. daily, delivered on the same schedule, with markedly lower systemic toxicity. In conclusion, the present study demonstrates that the new ceramide analogs II and V are characterized by in vitro and in vivo antitumor activity and low toxicity.

IT **322391-32-2P 379223-24-2P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and antitumor activity of ceramide analogs)

RN 322391-32-2 CAPLUS

CN 4(1H)-Pyrimidinone, 6-ethyl-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



RN 379223-24-2 CAPLUS
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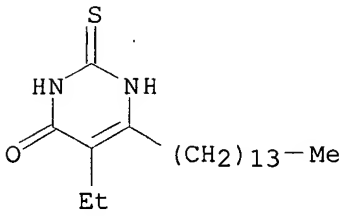

IT **322391-33-3P 379223-25-3P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antitumor activity of ceramide analogs)
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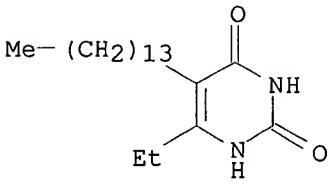
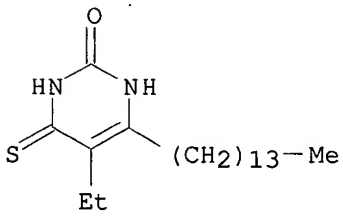


RN 379223-25-3 CAPLUS
CN 2(1H)-Pyrimidinone, 5-ethyl-3,4-dihydro-6-tetradecyl-4-thioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:78368 CAPLUS
DOCUMENT NUMBER: 134:131369
TITLE: process for the preparation of ceramide analogs and their use as antitumor agents
INVENTOR(S): Macchia, Bruno; Balsamo, Aldo; Macchia, Marco; Del Tacca, Mario; Danesi, Romano
PATENT ASSIGNEE(S): Bracco S.p.A., Italy
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007418	A2	20010201	WO 2000-EP7023	20000721
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 1307786	B1	20011119	IT 1999-FI169	19990722
EP 1198458	A2	20020424	EP 2000-956250	20000721
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PRIORITY APPLN. INFO.: IT 1999-FI169 A 19990722
WO 2000-EP7023 W 20000721
OTHER SOURCE(S): MARPAT 134:131369
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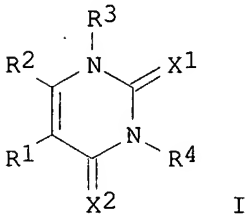

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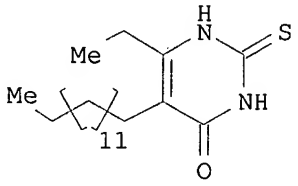


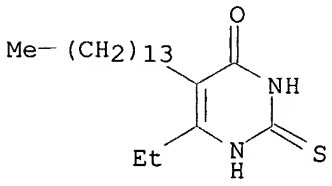
II

AB The present invention discloses a process for the prepn. of ceramide analog (I; X1, X2 = O, S; R1, R2 = (CH2)13Me, (un)substituted alkyl, (un)substituted alkylene groups with one or more substituents selected among arom., primary, secondary and tertiary aminic, quaternary ammonium, CO2H, OH, polyoxyalkyl and ethereal groups, amino acids, halogen, saccharidic portions, providing that between R1 and R2 only one is (CH2)13Me; R3, R4 = H, (un)substituted alkyl, (un)substituted alkylene groups with one or more substituents selected among arom., primary, secondary and tertiary aminic, quaternary ammonium, CO2H, OH, polyoxyalkyl and ethereal groups, amino acids, halogen, saccharidic portion) and

pharmaceutical formulations for the treatment of tumors. Thus, II was prepd. by the reaction of .beta.-ketoester III, Me(CH2)14CH(COCH2Me)COOCH2Me (obtained by the reaction of Et palmitate and propionyl chloride), with thiourea. II shows IC50 of 1.7 .mu.M in tests against human leukemia cell line called CCRF/CEM.

IT **322391-32-2P**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(process for the prepn. of ceramide analogs and their use as antitumor agents)

RN 322391-32-2 CAPLUS
CN 4(1H)-Pyrimidinone, 6-ethyl-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



IT **322391-31-1P 322391-33-3P 322391-34-4P**
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322391-38-8P 322391-39-9P 322391-40-2P
322391-41-3P 322391-42-4P 322391-43-5P
322391-44-6P 322391-48-0P 322391-51-5P
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322391-55-9P 322391-56-0P 322391-57-1P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the prepn. of ceramide analogs and their use as antitumor agents)

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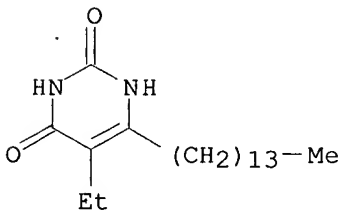

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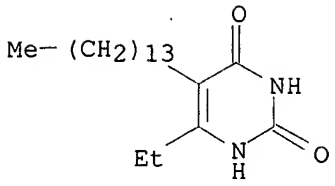

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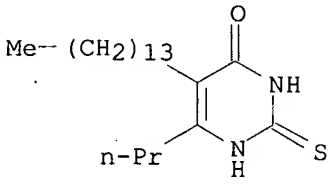

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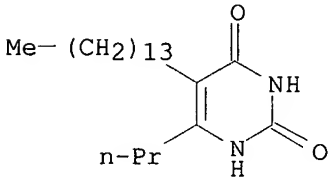

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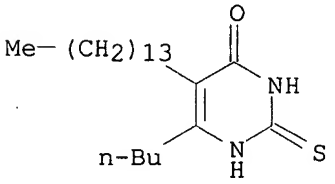

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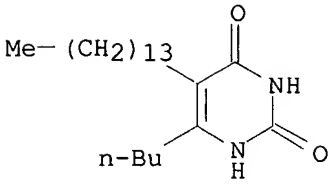

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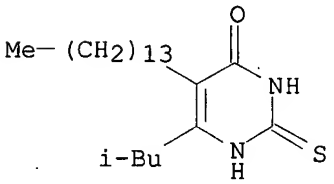

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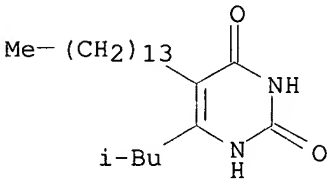

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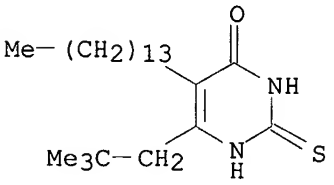
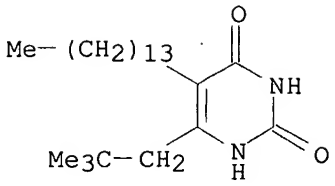
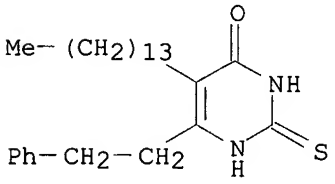


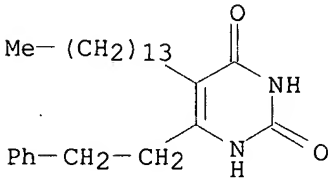
RN 322391-41-3 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 6-(2,2-dimethylpropyl)-5-tetradecyl- (9CI) (CA INDEX NAME)



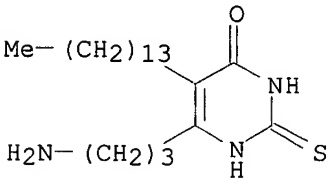
RN 322391-42-4 CAPLUS
CN 4(1H)-Pyrimidinone, 2,3-dihydro-6-(2-phenylethyl)-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



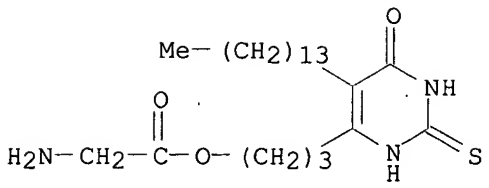
RN 322391-43-5 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 6-(2-phenylethyl)-5-tetradecyl- (9CI) (CA INDEX NAME)



RN 322391-44-6 CAPLUS
CN 4(1H)-Pyrimidinone, 6-(3-aminopropyl)-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)

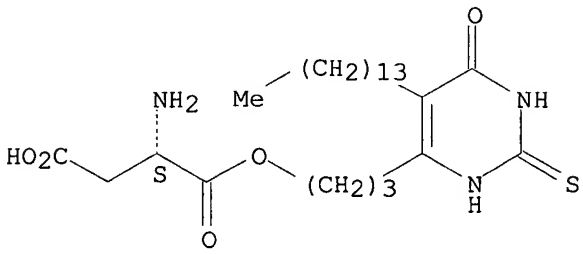


RN 322391-48-0 CAPLUS
CN Glycine, 3-(1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-4-pyrimidinyl)propyl ester (9CI) (CA INDEX NAME)



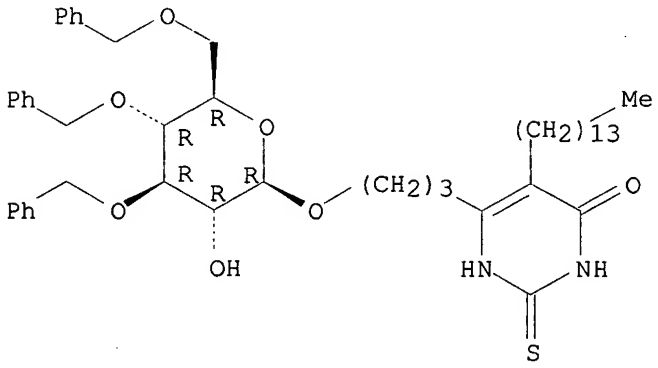
RN 322391-51-5 CAPLUS
CN L-Aspartic acid, 1-[3-(1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-4-pyrimidinyl)propyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

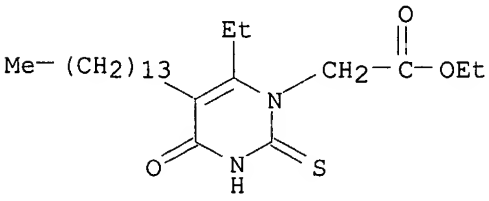


RN 322391-52-6 CAPLUS
CN 4(1H)-Pyrimidinone, 2,3-dihydro-5-tetradecyl-2-thioxo-6-[3-[[3,4,6-tris-O-(phenylmethyl)-.beta.-D-glucopyranosyl]oxy]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

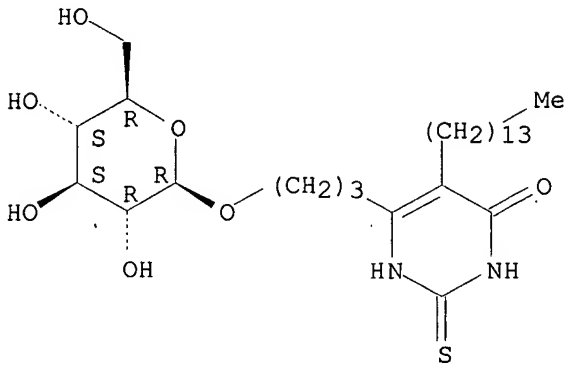


RN 322391-53-7 CAPLUS
CN 1(2H)-Pyrimidineacetic acid, 6-ethyl-3,4-dihydro-4-oxo-5-tetradecyl-2-thioxo-, ethyl ester (9CI) (CA INDEX NAME)

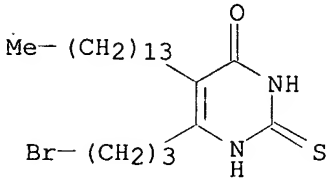


RN 322391-54-8 CAPLUS
CN 4(1H)-Pyrimidinone, 6-[3-(.beta.-D-glucopyranosyloxy)propyl]-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)

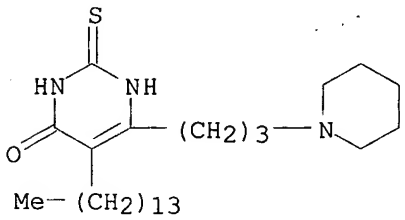
Absolute stereochemistry.



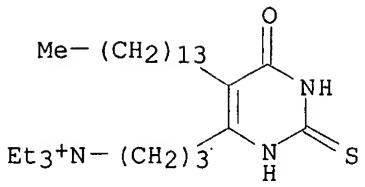
RN 322391-55-9 CAPLUS
CN 4(1H)-Pyrimidinone, 6-(3-bromopropyl)-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



RN 322391-56-0 CAPLUS
CN 4(1H)-Pyrimidinone, 2,3-dihydro-6-[3-(1-piperidinyl)propyl]-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)

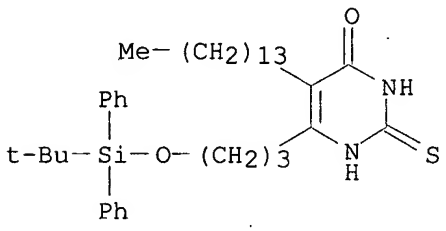


RN 322391-57-1 CAPLUS
CN 4-Pyrimidinepropanaminium, N,N,N-triethyl-1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-, bromide (9CI) (CA INDEX NAME)

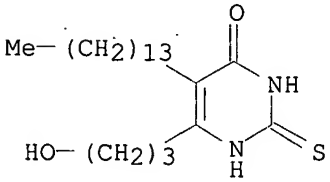


● Br^-

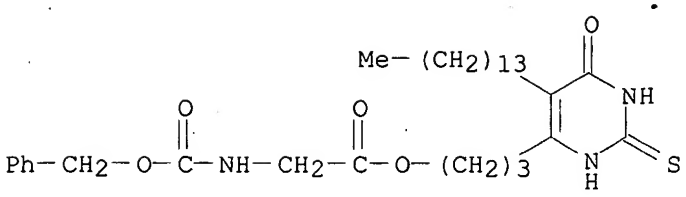
IT **322391-45-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the prepn. of ceramide analogs and their use as antitumor agents)
RN 322391-45-7 CAPLUS
CN 4(1H)-Pyrimidinone, 6-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



IT **322391-46-8P 322391-47-9P 322391-49-1P**
322391-50-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for the prepn. of ceramide analogs and their use as antitumor agents)
RN 322391-46-8 CAPLUS
CN 4(1H)-Pyrimidinone, 2,3-dihydro-6-(3-hydroxypropyl)-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)

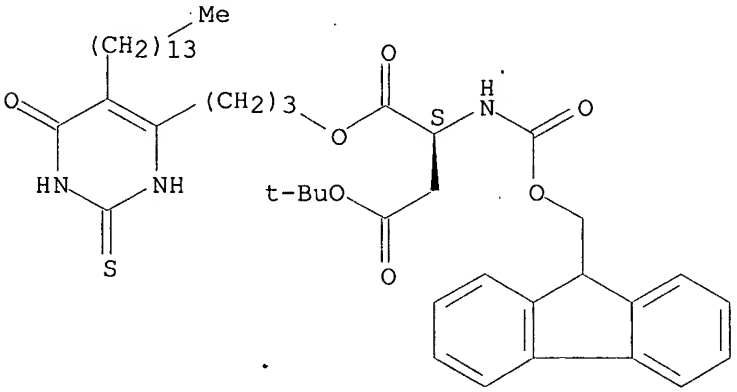


RN 322391-47-9 CAPLUS
CN Glycine, N-[(phenylmethoxy)carbonyl]-, 3-(1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-4-pyrimidinyl)propyl ester (9CI) (CA INDEX NAME)



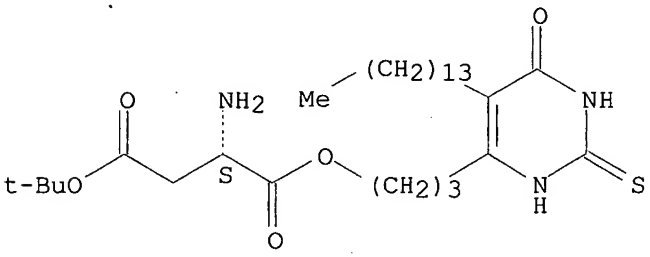
RN 322391-49-1 CAPLUS
CN L-Aspartic acid, N-[(9H-fluoren-9-ylmethoxy)carbonyl]-, 4-(1,1-dimethylethyl) 1-[3-(1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-4-pyrimidinyl)propyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



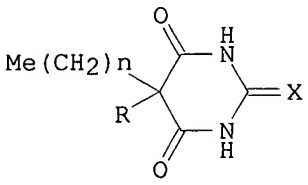
RN 322391-50-4 CAPLUS
CN L-Aspartic acid, 4-(1,1-dimethylethyl) 1-[3-(1,2,3,6-tetrahydro-6-oxo-5-tetradecyl-2-thioxo-4-pyrimidinyl)propyl] ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1981:156853 CAPLUS
DOCUMENT NUMBER: 94:156853
TITLE: Synthesis and antibacterial activity of high alkyl barbituric acids
AUTHOR(S): Beres, James A.; Kurlick, Nicholas J.; Shaffer, Scott E.; Varner, Max G.
CORPORATE SOURCE: Dep. Chem., Shippensburg State Coll., Shippensburg, PA, 17257, USA
SOURCE: Eur. J. Med. Chem. - Chim. Ther. (1980), 15(6), 571-3

CODEN: EJMCA5; ISSN: 0009-4374
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



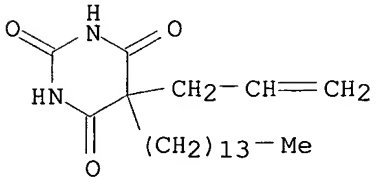
I

AB Barbituric acids I (R = allyl, n = 7, 11, 13, X = O; R = allyl, n = 11, X = S) were prepd. by alkylating di-Et allylmalonate and cyclizing the alkylallylmalonates with (H2N)2CX. I (n = 9, R = cyclopropylmethyl, X = O) was prepd. by treating di-Et decylmalonate with cyclopropylmethyl bromide and cyclizing with urea. I were less effective bactericides than the known I (R = allyl, n = 9, X = O).

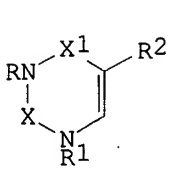
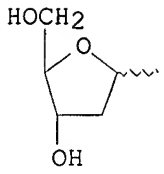
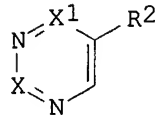
IT **77261-34-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and bactericidal activity of)

RN 77261-34-8 CAPLUS

CN 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-(2-propenyl)-5-tetradecyl- (9CI) (CA INDEX NAME)



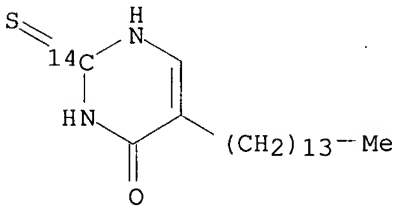
L19 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1979:152519 CAPLUS
DOCUMENT NUMBER: 90:152519
TITLE: Unnatural nucleosides and nucleotides. III. Preparation of 2- and 4-carbon-14-labeled 5-alkyluracils and 5-alkyl-2'-deoxyuridines
AUTHOR(S): Szabolcs, A.; Kruppa, G.; Sagi, J.; Otvos, L.
CORPORATE SOURCE: Cent. Res. Inst. Chem., Budapest, Hung.
SOURCE: J. Labelled Compd. Radiopharm. (1978), 14(5), 713-26
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI


I

III

IV

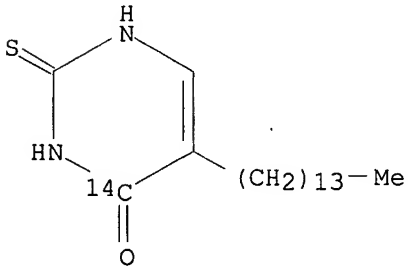
AB Uracils I (X = 14CO, X1 = CO, R = R1 = H)[R2 = Me, Me2CH (II), Me3C, Me(CH2)n (n = 1-7, 9, 13)] were prepd. (radiochem. yield 36.3-66.3%) by condensation of HC(OEt)3-Zn with R2CHBrCO2Et to give [R2CH[CH(OEt)2]CO2Et, followed by cyclocondensation with (H2N)214CS to thiones I (X = 14CS, X1, R-R2 as before), and oxidn. by (ClCH2CO2H, H2O). An analogous reaction sequence involving R2CHBr14CO2Et [R2 = Me, Et, Me(CH2)5, Me(CH2)13] and (H2N)2CS gave the corresponding uracils I (X = CO, X1 = 14CO, R = R1= H, R2 as above) (radiochem. yield 30-32, 32-35, 28-30, 24-25% resp). Uridines I (X = 14CO, X1 = CO; X = CO, X1 = 14CO)(R = H, R1 = .beta.-III; R = .alpha.-III, R1 = H)(R2 = alkyl) were obtained (major products R1 = .beta.-III) by condensation of the corresponding trimethylsilyl derivs. IV (X = 14COSiMe3, X = COSiMe3; X1 = 14COSiMe3)(R2 = alkyl) with 3',5'-di-O-p-chlorobenzoyl-.alpha.1.beta.-D-ribofuranosyl chloride in MeCN (HgBr2, room temp., 14 h) and deacylation (NaOMe). E.g., I (X = 14CO, X1 = CO, R2 = Me2CH)(R = H, R1 = .beta.-III; R = .alpha.-III, R1 = H) were obtained (radiochem. yield 45.6, 15.2%, resp. from II).

IT **69263-59-8P 69263-83-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and oxidative desulfurization of)

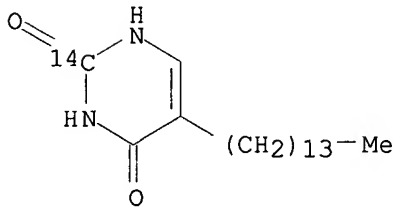
RN 69263-59-8 CAPLUS
CN 4(1H)-Pyrimidinone-2-14C, 2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



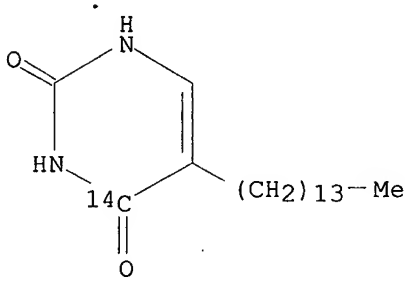
RN 69263-83-8 CAPLUS
CN 4(1H)-Pyrimidinone-4-14C, 2,3-dihydro-5-tetradecyl-2-thioxo- (9CI) (CA INDEX NAME)



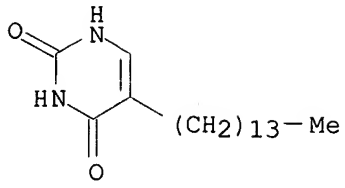
IT **69263-69-0P 69263-87-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and trimethylsilylation of)
RN 69263-69-0 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione-2-14C, 5-tetradecyl- (9CI) (CA INDEX NAME)



RN 69263-87-2 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione-4-14C, 5-tetradecyl- (9CI) (CA INDEX NAME)



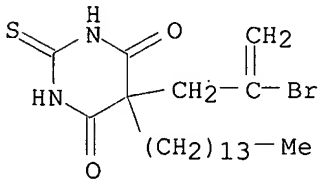
L19 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1976:31351 CAPLUS
DOCUMENT NUMBER: 84:31351
TITLE: Synthesis of 5-alkyl-2'-deoxyuridines
AUTHOR(S): Szabolcs, A.; Sagi, J.; Otvos, L.
CORPORATE SOURCE: Cent. Res. Inst. Chem., Hung. Acad. Sci., Budapest, Hung.
SOURCE: J. Carbohydr., Nucleosides, Nucleotides (1975), 2(3), 197-211
CODEN: JCNNAF
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Deoxyuridines I (R = alkyl) were prepd. in 55-90% yields by condensing the uracils II in MeCN using mol. sieves and HgBr2 with protected 2-deoxyribofuranosyl chloride followed by deblocking.
IT **57741-79-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and condensation of, with deoxyribofuranosyl chloride)
RN 57741-79-4 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 5-tetradecyl- (9CI) (CA INDEX NAME)



L19 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1968:87307 CAPLUS
DOCUMENT NUMBER: 68:87307
TITLE: 5-(.beta.-Bromoallyl)-5-tetradecyl-2-thiobarbituric acid
INVENTOR(S): Fahrni, Peter; Mosimann, Walter; Schnider, Otto
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co., A.-G.
SOURCE: Patentschrift (Switz.), 2 pp.
CODEN: SWXXAS
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CH 427819		19670714	CH	19620719

GI For diagram(s), see printed CA Issue.
AB Addn. to Swiss 411,901 (see Belg. 622,081, CA 59: 14006h). The title product (I), which is therapeutically compatible as the Na or Ca salt and is effective against virus infections, is made by the condensation of diethyl (.beta.-bromoallyl)tetradecylmalonate (II) with thiourea (III) in the presence of basic agents. Thus, 55 g. II was added to a soln. of 9.3 g. Na and 13.18 g. III in 90 ml. anhyd. MeOH and the mixt. stirred at 70.degree. 2 hrs. until a sample of the reaction soln. was clearly sol. in water to give I, m. 90.degree. (EtOH). The alkali salt is prepd. in alc. soln. with alkali alkoxide and the Ca salt by the reaction of the Na salt with CaCl2.
IT **17709-73-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 17709-73-8 CAPLUS
CN Barbituric acid, 5-(2-bromoallyl)-5-tetradecyl-2-thio- (7CI, 8CI) (CA INDEX NAME)



=> file caold; d que nos 120
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L20           1 SEA FILE=CAOLD ABB=ON  PLU=ON  L18
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L20  ANSWER 1 OF 1  CAOLD  COPYRIGHT 2002 ACS
ACCESSION NUMBER:  CA59:14006h  CAOLD
TITLE:             thiobarbituric acids
PATENT ASSIGNEE:   Hoffmann-La Roche, F., & Co. A.-G.
DOCUMENT TYPE:     Patent
     PATENT NO.    KIND         DATE
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PI   BE 622081
     FR 1342203
     FR M2059
     GB 973922
     US 3271402                 1966
INDEX TERM:       17709-73-8  22196-69-6  77261-33-7
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                  95001-08-4  95135-59-4  95221-65-1
                  95221-66-2  95222-46-1  95222-47-2
                  95564-75-3  95706-72-2  95808-74-5
                  95818-07-8
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     95222-46-1  95222-47-2  95808-74-5
     95818-07-8
RN   17709-73-8  CAOLD
CN   Barbituric acid, 5-(2-bromoallyl)-5-tetradecyl-2-thio- (7CI, 8CI)  (CA
     INDEX NAME)
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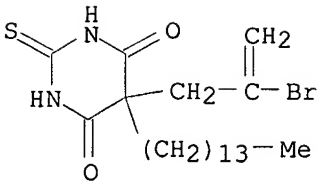

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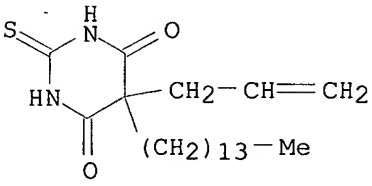

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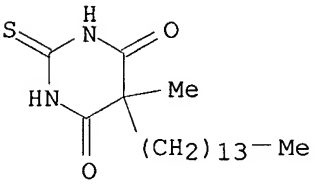

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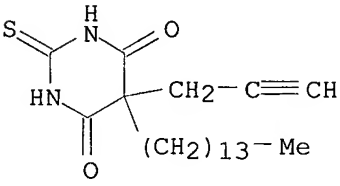

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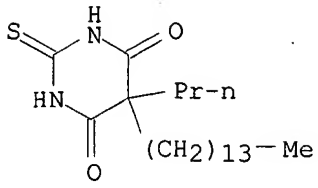

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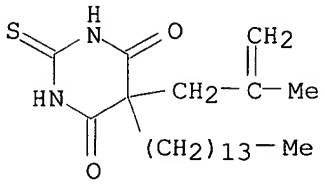

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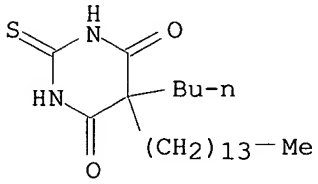

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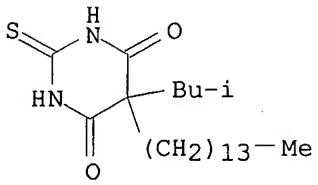

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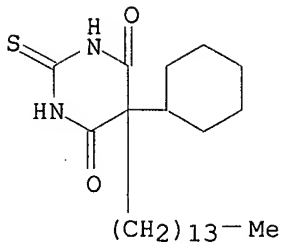

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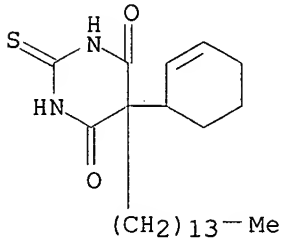

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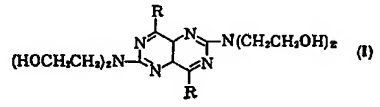
Thiamine disulfide tetrabenzoate. Chikataro Kawasaki. Japan. 11,634('63), July 9, Appl. Feb. 16, 1960; 2 pp. To a suspension of 2.5 g. thiamine disulfide in 50 cc. pyridine is added 5 cc. BzCl, the mixt. kept overnight, pyridine removed, the sirupy residue dissolved in AcOEt, washed with $NaHCO_3$ soln. and H_2O, and evapd. to give 2 g. title compd. (I), m. 97–100°, pale yellow sandy crystals, insol. in H_2O, sol. in EtOH, Me_2CO, and AcOEt. I is not decompd. by the aneurinase bacteria. Hiroshi Kataoka

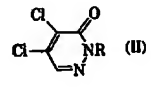
2,6 - Bis(diethanolamino)pyrimido[5,4 - *d*]pyrimidines. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,681 (Cl. 12*p*), June 27, 1963, Appl. Dec. 23, 1959; 2 pp. 2,6-Bis(diethanolamino)-4,8-bis(R-substituted)pyrimido[5,4-*d*]pyrimidines (I) are prepd. by treating 2,6-dichloro analogs (II) of I with diethanolamine (III) in the presence of an acid acceptor at 150–250°. Thus, 7.2 g. II (R = 1,2,5,6-tetrahydropyridino), m. 209–11° (decompn.), and 32 g. III are kept 50 min. at 190–5°, and the product taken up in 150 cc. H_2O and worked up to give 7.0 g. I (R = 1,2,5,6-tetrahydropyridino), m. 150–2° (repptd. from AcOH with AcONa, recrystd. from CH_2ClCH_2Cl). Similarly prepd. are these I (R, % yield, and m.p. given): 3-hydroxypiperidino, 57, 202–4°; 1,2,3,4-tetrahydroquinolino, 85, 223–5°; and these II (R and m.p. given): 3-hydroxypiperidino, 208–10°; 1,2,3,4-tetrahydroquinolino, 246–8°. Cf. Belg. 569,399.



(I)

A. Roders

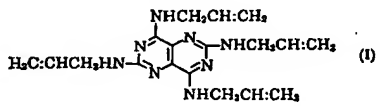
1-[(2-Chloroalkyl) and (2-chlorocycloalkyl)]-4,5-dichloro-6-pyridazones. Badische Anilin- & Soda-Fabrik A.-G. (by Franz Reicheneder and Karl Dury). Fr. 1,330,399, June 21, 1963; Ger. Appl. July 19, 1961; 12 pp. 1,4,5-Trichloro-6-pyridazone (I) is treated with alkenes and cycloalkenes to give the title compds. which can be used as herbicides and as insecticides. Thus, 5 parts I is added to 50 parts cyclohexene in portions at 60°, the mixt. agitated for 10 min., the excess cyclohexene evapd., and the residue recrystd. twice in MeOH to give 3 parts 1-(2-chlorocyclohexyl)-4,5-dichloro-6-pyridazone, m. 133–4°. Similarly prepd. are I (R and m.p. given): 2-chlorocyclooctyl, 99–



(II)

100° (cyclohexane); phenylchloroethyl, 134° (MeOH); dichloropropyl, 59° (ether); 2-bromocyclooctyl, 162–3° (cyclohexane); chloromethylpentyl, 39–40°; MeCHClCHMe, 51–3° (cyclohexane); chlorocyclododecyl, 87–9° (alc.); chloroisopentyl, 46–50° (petr. ether); $Me_2(MeO)CCHClCH_2$, 83–4° (petr. ether); $Me_2(AcO)CCHClCH_2$, 99–101° (MeOH); 5,5-dimethyl-4-chloro-2-dioxolanone-4-ylmethyl, 168–70° (MeOH); β-chloro-α-(2-pyrrolidon-2-yl)ethyl, 157–8° (MeOH); β-chloro-β-(9-carbazolyl)ethyl, 163–4° (MeCN); $Ph(ClCH_2)CMe$, 106–8° (MeOH); 2-chloro-5-cyclooctenyl, 151–3° (EtOH). Also prepd. is 1-(chlorocyclohexyl)-4-methoxy-5-chloro-6-pyridazone, m. 140–1°. BDPF

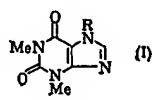
2,4,6,8 - Tetra(allylamino)pyrimido[5,4 - *d*]pyrimidine. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,084 (Cl. 12*p*), June 12, 1963, Appl. Apr. 25, 1956; 2 pp. Heating 5.4 g. 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine, 30 cc. allylamine, and 0.1 g. $CuSO_4$ in a sealed tube 1 hr. at 200°, then adding 200 cc. H_2O to the mixt. gave greasy material which solidified overnight. The yellow solid crystd. 3 times from dioxane gave the title compd. (I), m. 201–3°. I is useful as a vasodilator.



(I)

A. Nederlof

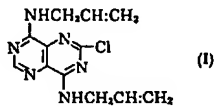
Theophylline and theobromine derivatives. Deutsche Gold und Silber-Scheideanstalt. Brit. 928,763, June 12, 1963; Ger. Appl. Aug. 16, 1958; 4 pp. Addn. to Brit. 859,445 (*CA* 55, 14489*d*). The title compds. were prepd. by reaction of an acetonyl deriv. of a xanthine with primary amines followed by catalytic redn. Thus, 23.6 g. 7-acetonyltheophylline was refluxed with 45.3 g. *dl*-norephedrine in 100 cc. abs. PhMe (with continuous removal of H_2O with BaO). On cooling, the reaction product was pptd. with petr. ether, filtered off, stirred with 1 l. hot H_2O, filtered off, dried, and recrystd. from EtOH to give 5.6 g., m. 169–70.5°, which was dissolved in 100 cc. EtOH and shaken with H at 60–70° at 80 atm. for 6 hrs. (Raney Ni). The catalyst was filtered off, pH adjusted to 5 with EtOH–HCl, the mixt. concd. *in vacuo*, and the product recrystd. (EtOH and EtO_2CCH_2Ac) to afford I [R = PhCH(OH)CHMeNHCH-



(I)

$MeCH_2$] HCl salt, m. 228–9°. Similarly prepd. were I [R = HO-$(CH_2)_2NH(CH_2)_2$] HCl salt, m. 195–8°; I [R = PhCH(OH)-$CHMeNH(CH_2)_2$] HCl salt, m. 249°; and 1-[2-(β-phenyl-β-hydroxyisopropylamino)ethyl]theobromine HCl salt, m. 242°. V. P. Arya

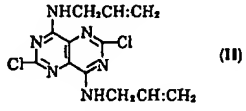
3-Chloropyrimido[5,4-*d*]pyrimidines. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,082 (Cl. 12*p*), June 12, 1963, Appl. Apr. 25, 1956; 2 pp. To 4.8 g. 2,4,8-trichloropyrimido[5,4-*d*]pyrimidine in 50 cc. dry dioxane was added 4.6 g. allylamine in 15 cc. dioxane. Addn. of H_2O gave 87% 2-chloro-4,8-bis(allylamino)pyrimido-



(I)

[5,4-*d*]pyrimidine (I), needles, m. 114–16° (EtOH); its 4,8-bis-(3-methoxypropylamino) analog m. 98–100°. These compds. are useful as vasodilators. A. Nederlof

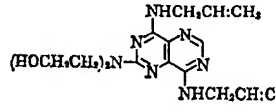
Pyrimido[5,4-*d*]pyrimidines. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,081 (Cl. 12*p*), June 12, 1963, Appl. Apr. 25, 1956; 2 pp. To 2.7 g. 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine (I) in 50 cc. dioxane was added 3.9 g. diallylamine in 20 cc. dioxane to ppt. an oil. The solvent evapd., the oil digested with dild. HCl, the whole stored, and the solid isolated and dried gave 97% 2,6-dichloro-4,8-bis(diallylamino)pyrimido[5,4-*d*]pyrimidine (II), fluorescent needles, m. 100–1° (MeOH). Similarly, 5.4 g. I in



(II)

70 cc. dioxane and 7.3 g. $HOCH_2CH(OH)CH_2NH_2$ in 70 cc. abs. alc. gave an oil, which treated with H_2O yielded 63% 4,8-bis(2,3-dihydroxypropylamino) analog of II, needles, m. 208–10° (H_2O). These compds. were useful as vasodilators. A. Nederlof

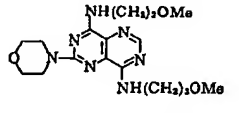
2-Diethanolamino-4,8-bis(allylamino)pyrimido[5,4-*d*]pyrimidine. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,085 (Cl. 12*p*), June 12, 1963, Appl. Apr. 25, 1956; 2 pp. Heating 4.2 g. 2-Cl analog of the title compd. (I) and 9.5 g. $HN(CH_2CH_2OH)_2$ 10 min. at 200°, digesting the oily mixt. with H_2O, and air-drying the ppt. (4.6 g.) crystd. from 0.1*N* HCl (C), then 3 times from H_2O gave I, needles, m. 104–6°. I is useful as a vasodilator.



(I)

A. Nederlof

2-Morpholino-4,8-bis(3-methoxypropylamino)pyrimido[5,4-*d*]-pyrimidine. Dr. Karl Thomae G.m.b.H. (by Franz G. Fischer, Josef Roch, and August Kottler). Ger. 1,150,086 (Cl. 12*p*), June 12, 1963, Appl. Apr. 25, 1956; 2 pp. The 2-Cl analog of the title compd. (I) (3.4 g.) and 3.5 g. morpholine heated in a



(I)

sealed tube 1 hr. at 200°, and the mixt. worked up gave 89% I, needles, m. 80–2° (addn. of 0.1*N* HCl, diln. with H_2O, then pptn. with concd. NH_4OH). This compd. is useful as a vasodilator. A. Nederlof

Thiobarbituric acids. F. Hoffmann-La Roche & Co., A.-G. Belg. 622,081, Mar. 4, 1963; Swiss Appl. Sept. 29, 1961; 13 pp. The title compds. (I) and their Na and Ca salts possessed therapeutic and prophylactic properties useful against the influenza virus, and were used in 100–1000 mg. dose. To a soln. of 16.5 g. Na in 162 ml. abs. MeOH, 23.2 g. thiourea was added, and the whole mixed to soln. To the soln. at 60°, 80 g. di-Et allyl-

(Ca OLD reference from L20 on p. 18